

Under reporting of Parkinson's disease on death certificates: a population-based study (NEDICES)

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ABSTRACT. Background: Parkinson's disease is frequently omitted as a cause of death from death certificates. A limitation of previous studies that attempted to assess the validity of death certificates is that population-dwelling cases, with milder, undiagnosed Parkinson's disease were likely excluded. As a result, those studies likely overestimated the validity of death certificates because they did not include these milder cases. We assessed the validity of death certificates in a prospective population-based study (NEDICES), which includes previously undiagnosed Parkinson's disease cases detected during the assessment.

Methods: 3,926 community-dwelling elderly subjects with and without Parkinson's disease were followed during a median of 12.6 years, after which the death certificates of those who died were examined. We calculated the proportion of cases of clinically diagnosed Parkinson's disease for whom a diagnosis of Parkinson's disease was certified as the basic cause of death on death certificates.

Results: 1,791 (45.6%) of 3,926 participants died over a median follow-up of 7.1 years, including 82 (73.9%) deaths among 111 participants with Parkinson's disease. Parkinson's disease was rarely certified as the basic cause of death (14.6%). Gender, disease stage and the period during which the study was conducted (i.e., 1994 to 2007) did not influence the likelihood that Parkinson's disease would be reported.

Conclusions: Our findings reinforce the notion that the reporting of Parkinson's disease on death certificates remains poor. This suggests a lack of awareness of the importance of Parkinson's disease as a cause of death.

INTRODUCTION

The burden of neurodegenerative diseases in high income countries is increasing, as the mean age of these populations increases. Parkinson's disease (PD) is one of the most common neurodegenerative disorders. With an increase in the prevalence of older people in recent decades, epidemiological and clinical information on PD becomes even more essential.[1] Two of the most relevant public health indicators are mortality rate and the cause of death. Death certificates have often been used as a source of data in order to understand the incidence, prevalence, and the mortality of PD,[2-6] as well as the causes of death associated with PD.[7, 8] However, the utility of such data may be limited.[9, 10] Often, death certificates do not accurately reflect the mortality of PD.[9] Previous studies have shown that PD is frequently omitted from the death certificate, even in cases with clear and long-standing PD.[9, 11-16]

A limitation of previous studies is that population-dwelling cases may not have been included. Therefore, it is likely that those studies overestimated the validity of death certificates because they did not include these milder cases.[9, 11-16] Our aim was to assess the validity of death certificates in a prospective population-based study (NEDICES), which includes previously undiagnosed Parkinson's disease cases detected during the assessment.

METHODS

Study population

Data for these analyses were derived from the Neurological Diseases in Central Spain (NEDICES) study, a longitudinal, population-based survey of the

prevalence, incidence, mortality, and determinants of major age-associated conditions of the elderly, including PD, essential tremor, stroke, and dementia.[17-27] Detailed accounts of the study population and sampling methods have been published.[28-30]

The survey area consisted of three communities: Margaritas (approximately 14,800 inhabitants), a working-class neighborhood in Getafe (Greater Madrid); Lista (approximately 150,000 inhabitants), a professional-class neighborhood in Salamanca district (Central Madrid), and Arévalo (approximately 9,000 inhabitants), the agricultural zone of Arévalo County (125 km northwest of Madrid). Up-to-date lists of residents were generated from population registers. In each community, survey eligibility was restricted to residents aged 65 years or older who were present there on December 31, 1993, or during 6 or more months of 1993. Eligible persons who had moved away from the survey area were not traced. In Margaritas and Arévalo, every eligible subject was to be screened. Because of the large number of elderly residents in Lista, proportionate stratified random sampling was used to select subjects for screening. All procedures were approved by the ethical standards committees on human experimentation at the University Hospitals “12 de Octubre” (Madrid) and “La Princesa” (Madrid). Written (signed) informed consent was obtained from all enrollees.

Study evaluation

Briefly, at the time of their baseline assessment (1994–1995), 5,278 elderly subjects were interviewed using a 500-item screening questionnaire that assessed demographic factors and medical conditions. The face-to-face interview included data collection on demographics, current medications (including drugs that affect the central nervous system), and medical conditions.

A short form of the questionnaire was mailed to subjects who declined or were unavailable for face-to-face interview, or telephone screening. This form collected data on demographic characteristics, several neurological disorders (essential tremor, stroke, dementia, and parkinsonism), current medications, and also requested the name of the subjects' family doctor.

The screening protocol for parkinsonism included three questions: (1) previous diagnosis of PD or parkinsonism, (2) complaint of tremor, (3) complaint of slowness.[17, 18] Participants were considered to have screened positive for parkinsonism if they responded positively to one or more question. Persons who screened positive for PD underwent a neurological examination, which was comprised of a general neurological examination and the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS).[31] The neurological examination was performed by one of eight senior neurologists who met at the inception of the study to establish standardized methods to perform and interpret the examination (J. B-L, F. B-P., and see <http://www.ciberned.es/estudio-nedices>). For subjects who could not be examined, medical records were obtained from their general practitioners, from in-patient hospitalizations, and from neurological specialists (if they had visited one). We defined parkinsonism based on four cardinal signs: resting tremor, rigidity, bradykinesia, and impaired postural reflexes.[17, 18] Parkinsonism was diagnosed when at least two signs were present in a subject not receiving anti-parkinsonian therapy, or when at least one sign was present in a patient specifically treated.[17, 18] Among subjects fulfilling these criteria, the etiologic subgroups were defined as follows:

Drug-induced parkinsonism was defined as an entity following the use of antidopaminergic drugs in the six months preceding onset of symptoms, along with a

previously negative history for the parkinsonian signs. The diagnoses were confirmed if the parkinsonian symptoms disappeared or subsided six months after stopping the drug, whenever it was possible.[17, 18]

Vascular parkinsonism was defined by the presence of at least two of the following findings: history of repeated strokes with abrupt onset and stepwise progression of parkinsonism features, hypertension, emotional incontinence and pseudobulbar palsy, broad-based rigid gait, and widespread pyramidal signs.[17, 18]

Parkinsonism with associated features, or due to other etiologies, such as nervous system infection, severe head trauma, brain tumor, dementia, or other neurological diseases that possibly affected the basal ganglia, was defined by routine clinical diagnosis.[17, 18] This type of parkinsonism also included Parkinson-plus syndromes.[17, 18]

Subjects were diagnosed as having definite PD or idiopathic parkinsonism after the exclusion of all other possible causes of parkinsonism. Unspecified parkinsonism was that for which clinical information was insufficient to reach an etiologic classification. A Hoehn and Yahr stage was assigned to each case.[32]

During the second (i.e., follow-up) evaluation (1997–1998), the same methods were used. Follow-up data on death were collected until May 1, 2007. The date of death was obtained from the National Population Register of Spain (*Instituto Nacional de Estadística*). In all Spanish communities, all deceased individuals receive the death certificate, completed by a doctor, at the time of death. In accordance with the recommendations of the World Health Organization, the classification of causes of death is based on the basic cause of death.[33] This is defined as the illness or injury which started the chain of pathological events which directly led to death.[33] The

certificate is then sent to the local authority in the municipality where the person had been living, and the information is collected in the National Register. The cause of death (using the International Classification of Diseases - ICD- 9th Revision for deaths occurred prior to 1999, and the ICD 10th Revision for deaths occurring thereafter) was divided into six primary categories: dementia, cerebrovascular disorders, cardiovascular disorders (pulmonary embolism, congestive heart failure, myocardial infarction, heart or aortic rupture, and asystole), respiratory diseases, cancer, and other causes (infections, trauma, genitourinary or gastrointestinal disorders).[33]

Statistical analyses

Data analyses were performed in SPSS Version 21.0 (SPSS, Inc., Chicago, IL). Unadjusted (bivariate) analyses were performed using the *t* test to compare mean ages and chi-square tests to determine associations between categorical variables.

We calculated the proportion of cases of clinically diagnosed PD for whom a diagnosis of PD was listed as the primary cause of death on the death certificate. To further determine whether PD was more likely to be certified in distinct subgroups of PD patients, we characterized the sample by age, gender, and PD stage. To identify the subject characteristics that were associated with having PD reported on death certificates, we performed a stepwise multiple logistic regression model with the dependent (outcome) variable being presence or absence of PD on the death certificate. Independent (predictor) variables eligible for inclusion in the model were gender (women [reference] vs. men), year of death (May 1, 1994 [reference] to September 30, 2001 vs. October 1, 2001 to May 1, 2007), and Hoehn and Yahr

stage (< 3 [reference] vs. \geq 3). These analyses generated odds ratios (OR) with 95% confidence intervals (CI).

RESULTS

Of the 5,278 participants screened for neurological disorders at baseline (1994-1995), we detected 81 prevalent PD cases, leaving 5,197 participants without baseline PD (Figure). Of these 5,197 participants, sufficient data were available on 3,845 who completed the follow-up evaluation (1997–1998), including 30 incident cases of PD.[17, 18]

To maximize the number of clinically diagnosed PD cases, we included data from the 30 incident cases as well as the 81 prevalent cases, even if some of the latter were not evaluated beyond the baseline assessment. Hence, the final sample of 3,926 participants included 111 PD cases and 3,815 non-PD cases (Figure).

The final sample of 3,926 participants was similar to the base sample of 5,278 participants in terms of gender (2,268 [57.8%] vs. 3,040 [57.6%] women, chi-square = 0.03, $p = 0.87$), and education (523 [13.4%] vs. 711 [13.6%] illiterate, chi-square = 5.42, $p = 0.14$), but it was, on average, 0.8 years younger (73.5 ± 6.6 vs. 74.3 ± 7.0 years, $t = 5.35$, $p < 0.001$).

The 3,926 participants had a mean duration of follow-up of 10.3 years (median = 12.6 years; range = 0.01 - 14.9 years). One-hundred-eleven (2.8%) of 3,926 participants were diagnosed with PD (81 at baseline and 30 at the second evaluation). Baseline demographic characteristics are shown (Table 1). Subjects with PD differed from those without PD in terms of age, gender and geographic area (Table 1).

1,791 (45.6%) of 3,926 participants died over a median follow-up of 7.1 years (range 0.03–13.3 years), including 82 (73.9%) deaths among 111 participants with PD and 1,709 (44.8%) deaths among 3,815 participants without PD.

Primary cause of death noted on the death certificates differed significantly by PD status (Table 2). PD was only rarely reported as the primary cause of death, even in the participants with PD (14.6%). In both groups, cardiovascular disease was the most frequently reported primary cause of death. Cancer was listed significantly less often in those with PD (14.6%) than in those without PD (24.2%).

Participants with PD in whom PD was reported (N = 12) were similar in age to those in whom it was not (N = 70) (77.1 ± 5.9 vs. 77.4 ± 5.6 years, $t = 0.15$, $p = 0.878$). They were also similar in gender (Chi Square test, $p = 0.320$).

Of the 82 PD participants who died, 80 (97.6%) had information on Hoehn and Yahr stage. PD was listed in a similar proportion of those with Hoehn and Yahr stage ≥ 3 (7, 20.6%) vs. those with Hoehn and Yahr stage < 3 (5, 20.9%) (Fisher's exact test, $p = 0.229$).

We divided our study period into two intervals, May 1, 1994 to September 30, 2001 and October 1, 2001 to May 1, 2007; this cut-point produced a similar number of deaths in each time interval (889 and 902, respectively). The two time intervals were similar in terms of the proportion of PD patients who were reported on death certificates: 14.5% vs. 14.8%, Fisher's exact test, $p = 0.974$.

Age at death, gender, year of death, and Hoehn and Yahr stage were not significantly associated with reporting PD on death certificates (data not shown) in the stepwise multiple logistic regression model. There was no evidence of lack of fit

in the final model according to the Hosmer-Lemeshow goodness-of-fit statistic ($p = 0.351$).

DISCUSSION

This is the first population-based study to investigate the validity of death certificates in terms of the listing of PD as a cause of death, which includes previously undiagnosed PD cases detected during the assessment. PD was reported in less than one-fifth (14.6%) of the certificates. This level of under-reporting is at the lower end of the range when compared with other studies that have examined the frequency of reporting PD on death certificates (20–70%).^[9, 11-16] As noted above, prior studies,^[9, 11-16] in not using a two-phase population-based are likely to have over-estimated validity.

Our results are in line with prior community-based surveys or clinical series.^[9, 11-16] In a clinical series of 253 PD patients who were recruited from the Odense University Hospital in Denmark and died within a period of 18 years, 70% of the death certificates had PD as a diagnosis.^[11] In one study involving one area of England and performed between 1966 and 1997, the authors showed that PD was recorded in death certificates of 130 (76%) of the 171 people (only 37% had PD coded as the underlying cause of death).^[12] In a prospective community-based study involving 245 PD from a defined geographical area in Norway, 84 died in the period ranging from 1993 until Dec 31st 1996.^[13] The death certificates showed that 47 (56%) of the total of 84 deceased PD patients in the study cohort had PD listed as a cause of death.^[13] In a series of 121 PD patients who were participating in a community-based study from a defined area of Sweden and died after 9.4 years of

follow-up, only 53% of the death certificates for the deceased patients recorded PD as an underlying or contributory cause of death.[14] In a national population-based survey from USA, among decedents with PD reported during life, 54.8% had PD recorded on the death certificate.[9] Nearly 70% of persons in higher income categories had PD recorded at death compared to 35.4% for those earning \$10,000 or less.[9] Age and gender adjusted odds of having PD recorded at death was 2.3 (1.1-3.9) for those with an annual income of \$35,000 or more.[9] In a prospective cohort of 143 PD patients under the care of the North Tyneside PD Service in UK, who died between January 1st 1999 and January 1st 2007, PD was recorded on the death certificate in 63% of patients.[15] Finally, in the 10-year follow-up data of the CamPaIGN study, death certificates indicated PD was a substantial contributor in only 20%.[16]

It is beyond the scope of this article to determine if the trend of decreasing risk of mortality of PD in different publications and studies based on death certificates is due to a real biological change or whether it merely reflects changes in reporting over time.[6]

The observation that cancer was listed significantly less often in those individuals with PD is of interest and is in line with the possible inverse occurrence of cancer and PD, similar to what has been noted for other conditions, such as cognitive impairment or Alzheimer's disease disease.[34, 35]

Our study has limitations. We did not collect data on the site of death and comorbidities at death, as well as data on who signed the death certificate (general physician vs. neurologist or geriatrician). It is logical to assume that the level of expertise of the physician signing the death certificate would impact upon the validity

of that certificate as in other neurodegenerative diseases, such as Alzheimer's disease.[33, 36] In addition, competing mortality is an issue to consider – PD patients are at risk of developing dementia, and therefore a diagnosis of dementia could have been certified as the basic cause of death on death certificates in some subjects in decrement of a diagnosis of PD. This study also has several strengths, including the large number of participants and its population-based design.

In conclusion, the results of the NEDICES study not only support those of previous studies,[9, 11, 13-16] but also reflect the need for a greater understanding and awareness by physicians, public health authorities, and other health management organs that PD should be considered as an important risk factor for increased mortality in older population.

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